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Review

The *Plasmodium* liver-stage parasitophorous vacuole: A front-line of communication between parasite and host

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ABSTRACT

The intracellular development and differentiation of the *Plasmodium* parasite in the host liver is a prerequisite for the actual onset of malaria disease pathology. Since liver-stage infection is clinically silent and can be completely eliminated by sterilizing immune responses, it is a promising target for urgently needed innovative antimalarial drugs and/or vaccines. Discovered more than 65 years ago, these stages remain poorly understood regarding their molecular repertoire and interaction with their host cells in comparison to the pathogenic erythrocytic stages. The differentiating and replicative intrahepatic parasite resides in a membranous compartment called the parasitophorous vacuole, separating it from the host-cell cytoplasm. Here we outline seminal work that contributed to our present understanding of the fundamental dynamic cellular processes of the intrahepatic malarial parasite with both specific host-cell factors and compartments.

1. Introduction

Malaria remains the most important vector-borne disease worldwide, leading to particular devastation in sub-Saharan Africa. Malaria-induced pathology is caused by the replication of single-celled parasites of the genus *Plasmodium* in the blood of infected individuals. Before entering the symptomatic infection of red blood cells, *Plasmodium* parasites undergo an obligatory and clinically silent developmental phase in the liver, which constitutes an ideal target for disease prevention (Prudencio et al., 2006; Rodrigues et al., 2012).

In order to establish the pathogenic erythrocytic stage of malaria, the intrahepatic parasite is highly replicative and differentiates into thousands of first-generation liver-stage merozoites (Prudencio et al., 2006). After parasite-induced death and detachment of the host cell, merozoite-filled vesicles, so-called merosomes, bud off into the sinusoid lumen (Sturm et al., 2006). The merosomes eventually burst and release the merozoites directly into the blood stream, where they can invade erythrocytes and thereby establish the pathogenic erythrocytic stage of malaria. Hence, intrahepatic development can be separated into distinct developmental phases: After successful penetration of the endothelial barrier in the liver sinusoid (Baer et al., 2007; Tavares et al., 2013) and transmigration of several liver cells (Mota et al., 2001), the infectious sporozoite eventually invades a suitable hepatocyte and concurrently forms a replication-competent niche known as the parasitophorous vacuole (PV) (Lingelbach and Joiner, 1998; Meis et al., 1983). The intracellular parasite then transforms into round-shaped, intracellular forms. A specific hallmark of the pre-erythrocytic intrahepatic phase is the repetition of closed mitosis ultimately leading to the formation of several thousand progeny. This development is exceptional for a eukaryotic obligate intracellular pathogen, and despite being metabolically active, the parasites likely depend on the extensive acquisition of host-cell factors (Allary et al., 2007; Deschermeier et al., 2012; Itoe et al., 2014; Meireles et al., 2017a,b; Tarun et al., 2008) in addition to relying on their own metabolism in order to ensure their survival and replication within host cells. Since the *Plasmodium* parasite does not reside freely in the host-cell cytoplasm or in endocytic compartments, but rather in a vacuole formed *de novo* during the active invasion process, nutrients have to cross the parasite plasma membrane as well as the parasitophorous vacuolar membrane (PVM).

It is well accepted that a complex, highly dynamic interplay between the host erythrocyte and the parasite exists for nutrient acquisition, turnover and waste removal, and furthermore, major modifications induced by the parasite to the host cell permit directed exchange of essential metabolites (Sherling and van Ooij, 2016). *Plasmodium* within red blood cells generate both tubular-like membranes connected to the PVM and independent intracytoplasmic membranous structures such as Maurer's clefts (Aikawa, 1971; Behari and Haldar, 1994; Hanssen et al., 2008; Matz et al., 2015a; Trager et al., 1966; Haldar

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et al., 2001; Lauer et al., 1997). It is suggested that the PVM is central to nutrient acquisition, host-cell remodeling, waste disposal, environmental sensing and, most importantly, it assists in protecting the intracellular pathogen from innate immune defences (Spielmann et al., 2012). However, we have still little knowledge about intrahepatic *Plasmodium* parasite stages with regard to interactions between the parasite and the host hepatocyte and their potential for nutrient uptake and/or exchange. In this review, we summarize recent advances in identifying host factors that promote or limit parasite intrahepatic development, and point out remaining gaps in our knowledge of host contributions to hepatic malaria infection.

2. General molecular players at the parasitophorous vacuolar membrane (PVM)

The PV is formed as *Plasmodium* sporozoites actively enter the host hepatocyte and are simultaneously surrounded by a membrane. The PV migrates to the perinuclear region of the hepatocyte, which is suggested to be the result of passive transportation caused by attachment of the PVM to the hepatocyte cytoskeleton (Graewe et al., 2012). The parasite quickly starts to modify the PVM with its own proteins to meet its needs (Kaushansky and Kappe, 2015; Prado et al., 2015). Because there is no signature PVM-targeting sequence, the identification of novel PVM-resident proteins remains difficult (Spielmann et al., 2012). Furthermore, the known *Plasmodium* PVM proteins lack homologs in other organisms and do not contain known functional domains, which complicates functional predictions. We will describe the molecular players at the PVM and summarize our current knowledge on PVM-resident proteins implicated in the recruitment of host cell factors followed by an overview about plasmodial proteins located at the PVM known so far (Fig. 1 and Table 1).

2.1. Host-factor recruiters – EXP1, UIS3, p36

Exported protein 1 (EXP1) was identified in 1983 and was the first protein shown to localize to the PVM and cytoplasmic parasite-derived vesicular inclusions in *P. falciparum*-infected erythrocytes (Adisa et al., 2003; Hall et al., 1983). More than ten years later it was found also in the PVM of liver-stage *P. falciparum* and *P. yoelii* (Sanchez et al., 1994; Charoenvit et al., 1995). Its N-terminal signal sequence contains the necessary information for trafficking the protein to the PV (Adisa et al., 2003), where it is incorporated with its N-terminus and C-terminus exposed to the PV lumen and host cell cytoplasm, respectively (Ansorge et al., 1997; Gunther et al., 1991). The same topology within the blood-stage PVM has been described also for members of the early transcribed membrane protein (ETRAMP) family (Curra et al., 2012; Spielmann et al., 2006). *P. falciparum* and *P. berghei* EXP1 were shown to be generally refractory to gene deletion or to promoter-swap approaches in the case of *P. berghei* suggesting that expression levels of this protein are vital for intraerythrocytic development (Maier et al., 2008; Sa e Cunha et al., 2017).

Interestingly, EXP1 might exert different functions during the liver and blood infection stages. EXP1 can act as a glutathione S-transferase, and evidence suggests it can degrade cytotoxic hematin generated in infected erythrocytes (Lisewski et al., 2014). During intrahepatic development EXP1 functions by recruiting the host-cell factor apolipoprotein H (ApoH), thereby facilitating successful liver-stage development (Sa e Cunha et al., 2017). The C-terminus of EXP1 was shown to

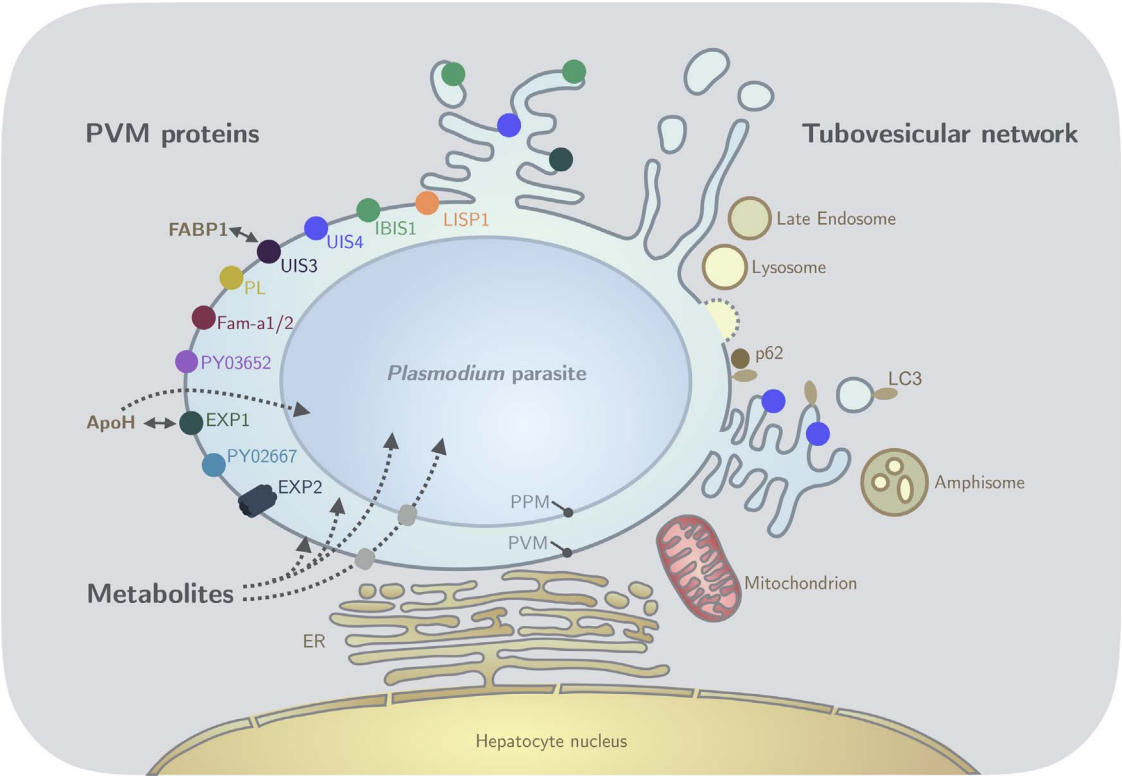

Fig. 1. The PVM of intrahepatic stages: a site for networking with the host cell.
The figure summarizes our current understanding on PVM-resident proteins, the liver-stage tubovesicular network, and the interaction with host cell factors and compartments.
PVM proteins: Highlighted are PVM-resident proteins identified thus far. UIS3 and the cross-stage protein EXP1 were shown to interact with host factors FABP1 and ApoH, respectively.
Tubovesicular network (TVN): The liver-stage TVN comprises extended tubovesicular structures emerging from the PVM, vesicular structures and highly dynamic tubules. The PVM and TVN associate with the host late endosomal and lysosomal compartments. Furthermore, the autophagy-related proteins p62 and LC3 together with ubiquitin (not shown) associate with the membranes surrounding intrahepatic parasites.
Metabolites: The fast-growing parasites in the liver acquire a plethora of nutrients such as cholesterol, phosphatidylcholine, lipoic acid, glucose, amino acids and metal ions to promote successful development.

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